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Summary Review of the Health Effects Associated with Zinc and Zinc Oxide

Health Issue
Assessment

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Health Issue Assessment

ENVIRONMENTAL CRITERIA AND ASSESSMENT
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Preface

The Office of Health and Environmental Assessment has prepared this summary health assessment to serve as a source document for EPA use. The summary health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of Zinc and Zinc Oxide as a hazardous air pollutant.

In the development of the summary health assessment document, the scientific literature has been inventoried through April 1987, key studies have been evaluated, and summary/conclusions have been prepared so that the chemicals' toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

Abstract

Zinc is a dense, bluish-white, relatively soft metal used extensively in the galvanizing of iron and steel. Zinc oxide, the most valued of the variety of compounds formed by zinc is used principally in rubber products as an activator in the vulcanization process and in the treatment of burns, infections, and skin diseases.

Zinc occurs naturally in the environment; however, zinc may also enter the environment as the result of mining and processing the production of zinc oxide and the manufacture and use of products containing zinc oxide, the combustion of coal and oil, the production of iron and steel, and the incineration of refuse.

Humans are mainly exposed to zinc through the ingestion of food (between 8 and 186 mg/kg/day) and drink (averaging up to 10 mg/day). Based on annual average airborne zinc concentrations in areas throughout the United States without mines or smelters of generally $< 1 \text{ mg/m}^3$, the contribution of zinc from inhaled air represents an insignificant amount of daily zinc exposure, averaging approximately 20 μg .

The literature on the toxic effects of zinc is limited. The most widely known systemic effect resulting from acute inhalation of freshly formed zinc oxide fumes is a disease called "metal fume fever." Metal fume fever occurs in certain occupational settings and the exposure level at which the fever occurs is not known. Also, the ingestion of zinc levels above 400 parts per million (ppm) produces acute gastrointestinal distress.

There is inadequate evidence to evaluate the carcinogenic potential of zinc or zinc oxide and no evidence suggesting that zinc is teratogenic. A definite conclusion regarding the possible reproductive or mutagenic effect of zinc cannot be drawn because of the lack of adequate studies.

Table of Contents

	<u>Page</u>
Preface	iii
Abstract	iv
Authors, Contributors, and Reviewers	vi
List of Tables	vii
1. Summary and Conclusions	1
2. Background Information	5
2.1 Chemical Characterization and Measurement	5
2.2 Sources and Emissions	5
2.3 Environmental Release and Exposure	6
2.3.1 Environmental Release	6
2.3.2 Exposure	7
2.4 Environmental Effects	8
3. Health Effects	10
3.1 Pharmacokinetics and Metabolism	10
3.1.1 Absorption	10
3.1.2 Distribution	13
3.1.3 Elimination	13
3.2 Essentiality and Biochemical Role	14
3.3 Clinical Manifestations of Zinc Deficiency	15
3.4 Effects in Animals	17
3.4.1 Acute Toxicity	17
3.4.1.1 Inhalation	17
3.4.1.2 Oral	19
3.4.2 Subchronic Toxicity	20
3.4.2.1 Inhalation	20
3.4.2.2 Oral	20
3.4.3 Chronic Toxicity	22
3.5 Carcinogenesis	22
3.6 Mutagenicity	23
3.7 Teratogenicity	24
3.8 Reproduction	24
3.9 Neurotoxicity	25
3.10 Effects in Humans	25
3.10.1 Inhalation Toxicity	25
3.10.2 Oral Toxicity	26
3.10.3 Other Routes of Exposure	27
3.10.4 Epidemiology	27
4. References	31

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List of Tables

<u>No.</u>		<u>Page</u>
2-1	Atmospheric emission factors	8
2-2	Acute toxicity values for fish	9
3-1	Typical zinc concentrations of normal tissues in four species	14
3-2	Recommended dietary allowances for zinc	15
3-3	Zinc metalloenzymes	16
3-4	Groups involved, age, duration of work and timing of work of the 66 workers exposed to the effect of zinc oxide--seen for medical examination	29

1. Summary and Conclusions

Zinc is a dense, bluish-white, relatively soft metal with an atomic weight of 65.37. Zinc oxide, the most valued of the variety of compounds formed by zinc, is a white or yellowish white, odorless, and tasteless powder with an atomic weight of 81.37.

In 1934, the U.S. mine production of zinc totaled 252,768 metric tons. Domestic production of zinc oxide in 1984 totaled 150,623 metric tons. Zinc is used extensively in the galvanizing of iron and steel. Zinc oxide is used principally in rubber products as an activator in the vulcanization process. One of the oldest uses of zinc oxide is in the treatment of burns, infections, and skin diseases.

In soils, the zinc content ranges from 10 to 300 $\mu\text{g/kg}$. Uncontaminated fresh water generally contains $< 10 \mu\text{g zinc/L}$. In sea water, the zinc content ranges from 1 to 27 $\mu\text{g/L}$.

In addition to the naturally occurring levels of zinc in the environment, there are manmade sources which enter the environment as contaminants. Such sources include mines, smelters, production of zinc oxide and the manufacture and use of products containing zinc oxide, the combustion of coal and oil, the production of iron and steel, and the incineration of refuse.

Limited data are available on ambient air levels around mines or smelters; however, it has been estimated that 100 g of zinc is emitted to the atmosphere per metric ton of zinc mined and milled. Air concentrations of zinc have been reported to range from 0.27 to 15.7 $\mu\text{g/m}^3$ over 24-hr periods proximal to one U.S. smelter in 1977. The annual average around that smelter in 1977 was 5.0 $\mu\text{g/m}^3$. However, average yearly or quarterly atmospheric zinc levels of $< 1 \mu\text{g/m}^3$ have been reported for several other areas with smelters; and in areas without mines or smelters, ambient air levels of zinc generally average $< 1 \mu\text{g/m}^3$.

High levels of zinc in surface waters represent industrial and urban pollution from such sources as galvanized pipes, dumpings of plating baths, and zinc mining. Surface water has been found to contain zinc levels as high as 21.0 mg/L as the result of the disposal of zinc mining waste. Water leaving treatment plants generally contains $< 5 \text{ mg/L}$ of zinc.

Zinc is toxic to aquatic organisms and other wildlife at high exposure levels. In aquatic organisms, zinc toxicity depends largely on the water hardness and pH, as well as the exposure level.

Several quantitative methods may be used for determining the atmospheric and soil levels of zinc and zinc compounds. The analytic techniques frequently used are X-ray fluorescence spectrometry (X-ray emission spectrometry), neutron activation analysis, mass spectrometry, voltammetry, absorption spectrophotometry, atomic absorption spectrometry, atomic fluorescence spectrometry, and optical emission spectroscopy. The preferred method for analysis of zinc and zinc compounds in water is anodic stripping voltammetry.

The body of a 70-kg man typically contains approximately 1.4 to 2.3 g of zinc. Humans are mainly exposed to zinc through the ingestion of food

and drink. The zinc content of the average daily diet ranges from 8 to 18.6 mg/kg. The ingestion of 2 liters of water per day could contribute up to 10 mg zinc per day. The contribution of zinc from inhaled air represents an insignificant amount of the daily zinc exposure, averaging approximately 20 μ g. Zinc may also be absorbed through skin during the administration of ointments containing zinc oxide or from skin contact with dust containing zinc.

Inhaled zinc is absorbed across the alveolocapillary membrane; however, the fate of inhaled zinc will depend on the particle size and solubility as well as the functional state of the lungs. There are no quantitative data on the deposition and absorption of inhaled zinc compounds, but experiments on humans indicate that both zinc oxide dust and fumes of very small particle size are deposited in the alveoli. That inhaled zinc is absorbed was shown by the finding of widespread distribution of zinc in the soft tissue and liver of a man accidentally exposed to radiolabeled zinc dust from an experimental reactor and increased plasma and serum zinc levels in exposed workers.

Orally administered zinc is absorbed at several loci in the gastrointestinal tract, particularly in the second portion of the duodenum. The rate of absorption depends on the level and form of zinc administered and the presence or absence of other substances.

Zinc is mainly excreted via the gastrointestinal tract; approximately 70 to 80 percent of the ingested zinc is found in the stool. To a lesser extent, zinc is eliminated via urine, sweat, hair, and skin. Urinary excretion of zinc may be substantial in certain disease states.

Numerous studies indicate that the body attempts to control the zinc balance homeostatically by regulating zinc absorption and fecal excretion. The mechanism governing this homeostatic regulation is not well understood; however, available data suggest that several proteins and some low-molecular-weight compounds may be involved.

Zinc is essential for the growth and development of both plants and animals and has been included in the list of recommended dietary allowances (RDA) for humans. A daily intake of 15 mg/day has been recommended for adults and 10 mg/day for preadolescent children. In children ages 0.5 to 1.0 year, 5 mg/day has been recommended and 3 mg/day for infants ages 0 to 6 months. A daily zinc intake of 20 and 25 mg/day is recommended for pregnant and lactating women, respectively. Zinc deficiency in people can result in dwarfism, anemia, hypogonadism, hepatosplenomegaly, rough and dry skin, and mental lethargy. From a public health perspective, much greater concern generally exists in regard to zinc deficiency associated with insufficient daily intake of the metal in contrast to toxic effects less often seen in association with excessive intake resulting from higher level exposures to zinc in food, water, or air.

The literature on toxic effects resulting from exposure to zinc is very limited. The most widely known systemic effect resulting from acute inhalation of freshly formed zinc oxide fumes is a disease called "metal fume fever." Metal fume fever occurs in certain occupational settings and generally strikes at the beginning of the work week when the worker has not been exposed for several days. It is characterized by headache, fever, hyperpnea, nausea, sweating, and muscle pains, which occur within a few hours after exposure and persist for 1 to 2 days. The exact acute exposure level at which metal fume fever occurs is not known, but it has been estimated that metal fume fever generally does not occur at zinc oxide levels below 15 mg/m³, although some Eastern European literature reports the occurrence of metal fume fever in workers repeatedly exposed to zinc oxide levels averaging as low as 5 mg/m³ but ranging up to 58 mg/m³. Chronic

respiratory infection, dermatitis, conjunctivitis, and gastritis were also reported for the same workers. Other Eastern European literature reported an increase in respiratory illnesses such as chronic bronchitis and diffuse pneumosclerosis in workers exposed to zinc oxide levels of up to 5.1 mg/m³. However, in both reports, contributions from other substances in the workplace air cannot be ruled out. Hypocalcemia was reported in workers exposed to zinc oxide levels ranging from 2.44 to 7.15 mg/m³.

The National Institute for Occupational Safety and Health (NIOSH) has sought to protect workers exposed to zinc oxide fumes by recommending an exposure standard. Occupational exposure to zinc oxide fumes shall not exceed concentrations greater than 5 mg zinc oxide/m³ determined as a TWA exposure for up to a 10-hour workday, 40-hour workweek, with a ceiling of 15 mg zinc oxide/m³ as determined by a sampling time of 15 minutes. The Occupational Safety and Health Administration (OSHA) established an 8-hour TWA permissible exposure limit of 5 mg zinc oxide/m³ and the American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a threshold limit value (TLV) of 5 mg/m³.

Acute effects also result from exposure to zinc chloride, the major component of smoke bombs. Inhalation of this smoke in confined areas has resulted in severe pulmonary disease and death. No information is available on the concentrations of zinc chloride which causes these effects.

The ingestion of zinc levels above 400 ppm is known to cause acute gastrointestinal distress. Such conditions usually result from the ingestion of food and/or drink which has been stored in galvanized containers. However, epigastric pain has been reported in subjects chronically exposed to mean zinc oxide levels of 5 to 18 mg/m³ in an occupational setting. Available information also suggests that the administration of 150 mg elemental zinc/day for 6 weeks may have an adverse effect on the immunologic and cardiovascular systems.

Zinc oxide has been shown to cause chromosomal damage in the form of an increased frequency of hyperdiploid cells in the bone marrow of noninbred white rats at concentrations of 0.1 and 0.5 mg/m³. An increase in the frequency of structural aberrations of the chromosomes and hyperdiploid cells was seen when human lymphocytes at the G₀ stage of the cell cycle were exposed to zinc acetate at concentrations of 7.0 to 20.0 µg/mL. An interpretation of this report is difficult because the category of aberrations referred to as hyperdiploid cells is not one generally used by cytogeneticists in discussing this type of study. Additionally, the frequency of structural aberrations at 20 µg/mL was slightly less than the frequency at 7 µg/mL. Zinc oxide was not mutagenic at levels of 100 to 5,000 µg/plate in the Salmonella reversion assay.

There are no data which suggest that a zinc level over that required for normal growth and development is teratogenic. A greater risk of malformations is expected in regard to zinc deficiency. Zinc also appears to offer a degree of protection against the teratogenic effect of cadmium. There are several animal studies and one human study which suggest that the ingestion of high levels of zinc may have an adverse impact on reproduction. Three premature births and one stillbirth occurred in a small group of women ingesting 40.5 mg zinc/day during the third trimester of pregnancy. However, no adverse effects on the outcome of pregnancies were observed in a group of women supplemented with 81 mg zinc/day during the third trimester of pregnancy.

There is no evidence suggesting that inhaled zinc or orally or parenterally administered zinc induces tumor formation. The only positive carcinogenic

response resulting from zinc exposure occurs following injection of zinc salts into the testes of fowl and rats. Since this route of exposure is not likely to be encountered by humans, the predictive value of these results for humans is limited given the lack of carcinogenicity testing and epidemiologic studies. The available evidence for zinc is considered to be inadequate to assess the carcinogenic potential equivalent to a Group D weight of evidence. There are, however, data which indicate that zinc is indirectly involved in tumor formation as a growth promoter or inhibitor. In some animal studies, zinc-deficient diets have been found to promote the development of chemically induced cancers, whereas zinc-adequate and zinc-supplemented diets provide a protective barrier against tumor formation. In other animal studies, zinc-adequate or zinc-supplement diet facilitated the development of chemically induced cancers. Also, examinations of cancerous tissues in humans have shown that the zinc level deviates from that found in noncancerous tissue.

2. Background Information

This overview provides a brief summary of the data available on the health effects of exposure to zinc/zinc oxide. Emphasis is placed on determining whether there is evidence to suggest that zinc/zinc oxide exerts effects on human health under conditions and at concentrations commonly experienced by the general public. Both acute and chronic effects are addressed, including general toxicity, teratogenicity, mutagenicity, and carcinogenicity. To place the health effects discussion in perspective this report also reviews certain air quality aspects of zinc/zinc oxide in the United States, including sources, distribution, fate, and concentrations associated with rural, urban, and point source areas. This report draws from earlier reviews of the subject area (National Research Council, 1978; U.S. Environmental Protection Agency, 1980) and summarizes findings from more recent primary sources as well.

2.1 CHEMICAL CHARACTERIZATION AND MEASUREMENT

Zinc has the molecular formula Zn. It is a dense, bluish-white, relatively soft metal with an atomic weight of 65.37.

Zinc oxide, also known as flowers of zinc, zinc white, Chinese white, philosopher's wool, and zincite is the most valued of all the compounds formed by zinc. It is a white or yellowish white, odorless, and tasteless powder with the molecular formula ZnO and atomic weight of 81.37.

Several quantitative methods may be used to determine atmospheric and soil levels of zinc and zinc oxide. These include X-ray fluorescence spectrometry (X-ray emission spectrometry), neutron activation analysis, mass spectrometry, voltammetry, absorption spectrophotometry, atomic absorption spectrometry, atomic fluorescence spectrometry, and optical emission spectroscopy (National Research Council, 1978). The preferred analytical technique for determination of zinc in water is anodic stripping voltammetry (Nriagu, 1980a).

2.2 SOURCES AND EMISSIONS

In the United States there are over 25 mines and smelters where zinc is produced and processed. In 1984, 252,768 metric tons of zinc were mined in the U.S., with a worldwide mine production of 6,419,000 metric tons. Domestic production of zinc oxide in 1984 totaled 150,623 metric tons. Primary and secondary smelter production totaled 331,245 metric tons (Jolly, 1985). Currently there are four basic types of primary zinc smelters in the U.S.: horizontal retort distillation units, vertical retort distillation units, electrolytic plants, and electrothermic plants (Lloyd and Showak, 1984; Nriagu, 1980a; Jolly, 1985).

Because of its electrochemical nature, zinc is used extensively to galvanize iron and steel. The element also readily combines with other metals, imparting the characteristics of workability at low temperatures; corrosion resistance; and pleasing finishes for use in die-casting alloys.

brass, and other common alloys. Zinc displays a vigorous reducing power, liberating hydrogen from sulfuric and hydrochloric acid. This property is the basis for the use of zinc dust or mossy zinc in many commercial organic chemical processes (National Research Council, 1978; Nriagu, 1980a).

Zinc oxide is principally used to activate the vulcanization of rubber. It also helps protect rubber by its opaqueness to ultraviolet light and its high thermal conductivity. A newer use of zinc oxide utilizes its photoconductive and electrostatic properties in office photocopying applications (National Research Council, 1978; Nriagu, 1980a). One of the oldest uses of zinc oxide is in the treatment of burns, infections, and skin diseases (McKay, 1983; National Research Council, 1978; Nriagu, 1980a). It is also used to give white paints good concealing power, in the manufacture of opaque and certain types of transparent glass, and in the manufacture of porcelain enamels for sheet iron and vitreous enamels for cast iron (National Research Council, 1978; Nriagu, 1980a).

2.3 ENVIRONMENTAL RELEASE AND EXPOSURE

2.3.1 Environmental Release

Although zinc is a moderately abundant element in nature, it does not occur in the free state but instead is found as a salt or oxide. Zinc levels occur around $70 \mu\text{g/kg}$ in the earth's crust. Some zinc is present in part in igneous and metamorphic rock as the sulphide sphalerite. In sedimentary rock, zinc is concentrated notably in shale and clays. It is also quite concentrated in marine phosphorites (National Research Council, 1978; Nriagu, 1980a). In soils, the zinc concentration ranges from 10 to $300 \mu\text{g/kg}$. Naturally occurring levels of zinc in fresh water and sea water are <10 and from 1 to $27 \mu\text{g/L}$, respectively (National Research Council, 1978; Lloyd and Showak, 1984). Background ambient levels of zinc have been measured over the South Pole and the Atlantic Ocean. An average concentration of 0.03 ng/m^3 was found over the South Pole. Zinc levels over the Atlantic Ocean ranged from 0.3 to 27 ng/m^3 (U.S. Environmental Protection Agency, 1980; Nriagu, 1980a). In addition to the naturally occurring levels of zinc in air, zinc is also emitted to the atmosphere from such man-made sources as: zinc mining, milling, and concentrating; metallurgical processing; the production of zinc compounds; and the manufacture and use of the products containing zinc (National Research Council, 1978; U.S. Environmental Protection Agency, 1980; Lloyd and Showak, 1984; Nriagu, 1980a).

Loss of zinc from mining is small, but some does occur during blasting, ore handling, crushing, and wind loss from tailings. Only limited data were found on the concentrations of atmospheric zinc near mines; however, it has been estimated that 100 g of zinc is emitted to the atmosphere per metric ton of zinc mined and milled (W. E. Davis and Associates, 1972; Lloyd and Showak, 1984; Nriagu, 1980a). On the basis of the 1984 total of 252,768 metric tons of zinc mined and milled in the U.S., the total zinc emissions to the atmosphere from this process would be 25 metric tons.

During the smelting process zinc may be released to the atmosphere during concentrate handling, open storage, and conveying. Roasting could also create large amounts of zinc dust, but since this operation is enclosed, the dust may be readily collected using particulate collecting devices which recover >95 percent of the particulate matter (National Research Council, 1978; Nriagu, 1980a; Lloyd and Showak, 1984). There are only limited data on levels of atmospheric zinc near smelters. In 1977, a yearly mean zinc level of $5 \mu\text{g/m}^3$ was found approximately 1.5 miles from a smelter in Kellogg,

Idaho. The 24-hour values ranged from 0.27 to 15.7 $\mu\text{g}/\text{m}^3$ (U.S. Environmental Protection Agency, 1980). The U.S. Environmental Protection Agency (Hunt et al., 1984) reported average yearly or quarterly zinc concentrations of $<1 \mu\text{g}/\text{m}^3$ in several areas with smelters. Table 2-1 lists other emission factors and sources of zinc.

Available data on atmospheric levels of zinc have shown a general decline. The National Air Sampling Network reported annual average airborne zinc concentrations in areas throughout the U.S. without mines or smelters of generally $<1 \mu\text{g}/\text{m}^3$ (U.S. Environmental Protection Agency, Hunt et al., 1984; National Research Council, 1978). Atmospheric zinc levels in the Washington, D.C. area ranged from 0.05 to 0.1 $\mu\text{g}/\text{m}^3$ (Kowalczyk et al., 1982). Lee and von Lehmden (1973) reported atmospheric zinc levels in urban areas throughout the U.S. of 0.1 to 1.7 $\mu\text{g}/\text{m}^3$. In 1970, the average atmospheric zinc level in urban areas in the U.S. ranged from 0.1 to 1.7 $\mu\text{g}/\text{m}^3$ (Lee et al., 1972). Dyson and Quon (1976) reported average atmospheric zinc levels in urban air in 1966 of 0.7 $\mu\text{g}/\text{m}^3$.

Zinc levels in water are generally very low. High levels of zinc in surface water represent industrial and urban pollution from such sources as galvanized water pipes, dumping of plating baths, and zinc mining (National Research Council, 1978; U.S. Environmental Protection Agency, 1980; Nriagu, 1980a). In a 16-month study, Mink et al. (1971) found that a section of Idaho's Couer d'Alene River system contained zinc levels of up to 21 mg/L as the result of the disposal of zinc mining waste for a number of years. The U.S. Department of Health, Education, and Welfare (currently the Department of Health and Human Services) found that, of 2,595 drinking water samples, 8 samples contained zinc levels above 5 mg/L. Water leaving treatment plants generally contains less than 5 mg/L of zinc, but in cities with soft acidic water, the level of zinc increases in the distribution system. Therefore, tap water could contain zinc levels of around 5 mg/L (U.S. Environmental Protection Agency, 1980).

Atmospheric workplace concentration limits have been established for zinc oxide. The Occupational Safety and Health Administration (OSHA) established an 8-hour time-weighted average (TWA) permissible exposure limit of 5 mg zinc oxide/ m^3 and the American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a threshold limit value (TLV) of 5 mg/ m^3 . The National Institute for Occupational Safety and Health (NIOSH) has recommended the following standard. Occupational exposure to zinc oxide fumes shall not exceed concentrations greater than 5 mg zinc oxide/ m^3 determined as a TWA exposure for up to a 10 hour workday, 40 hour workweek, with a ceiling of 15 mg/ m^3 as determined by a sampling time of 15 minutes.

2.3.2 Exposure

Humans are exposed to zinc through the inhalation of air and the ingestion of food and water. Zinc levels in air are generally $<1 \mu\text{g}/\text{m}^3$ (U.S. Environmental Protection Agency, 1984; National Research Council, 1978). Assuming an individual inhales 20 m^3 of air per day with an average zinc concentration of 1 $\mu\text{g}/\text{m}^3$, the daily zinc contribution from this source would be 20 μg .

There is a wide range of values published in the literature on the zinc content of various foods; however, in general, meat, milk products, eggs, shellfish (Halsted et al., 1974; National Research Council, 1978; U.S. Environmental Protection Agency, 1980; Nriagu, 1980b) and wheat germ

TABLE 2-1. Atmospheric Emission Factors

Source	Emission Factor
Mining (Zn + Cu + Pb)	100 g/metric ton
Primary metal production	
Zinc	17,600 g/metric ton
Lead	110 g/metric ton
Copper	845 g/metric ton
Nickel	845 g/metric ton
Aluminum	11 g/metric ton
Secondary metal production	
Zinc	9,000 g/metric ton
Copper	500 g/metric ton
Lead	300 g/metric ton
Iron and steel	27 g/metric ton
Ferroalloys and iron foundaries	54 g/metric ton
End uses of zinc products inadvertent sources	
Coal combustion	4.8 g/metric ton
Oil combustion	0.025 g/metric ton
Wood combustion	58 g/metric ton
Waste incineration	500 g/metric ton
Rubber tire wear	4.5 g/tire
Phosphate fertilizers	15 g/metric ton
Grain handling	0.5 g/metric ton

Source: Nriagu (1980a)

(National Research Council, 1978) are the best sources of dietary zinc. Halsted et al. (1974) reported a zinc content of standard hospital diets (breakfast, lunch, and dinner) of 11.3 mg. The U.S. Environmental Protection Agency (1980) reported a zinc dietary intake of 18 and 18.6 mg/day for males ages 15 to 20 years old, respectively, whereas the daily dietary intake of girls 12 to 14 years old was 10 mg. Nriagu (1980b) reported daily zinc dietary intakes of 8 to 14 mg.

Zinc levels in water are usually very low; however, due to contamination, levels of 5 mg/L have been reported (U.S. Environmental Protection Agency, 1980). Assuming an individual ingests 2 liters of water per day containing 5 mg zinc/L, the daily intake of zinc from drinking water would be 10 mg.

2.4 ENVIRONMENTAL EFFECTS

Zinc levels above those needed for maximal plant growth may produce toxic effects. Buchauer (1973) reported that the vegetation around two smelters in Palmerton, PA was scrubby, with red and yellow foliage and interveinal chlorosis. Depressed yield and leaf damage ranging from marginal

necrosis to death was seen in legumes exposed to 3.2 and 6.25 μM zinc in a flowing culture system (Carroll and Loneragan, 1968). Nriagu (1980a) reported that excessive levels of zinc curtails growth in plants by inhibiting root development through restraint on both cell division and elongation.

Aquatic toxicity appears to depend largely on the water hardness and pH, as well as the exposure level (Brungs, 1969; Pickering and Henderson, 1966; Nriagu, 1980a). Gasaway (1972), in an effort to determine the cause of death of ducks, geese, and swans in the Couer d'Alene Lake area where zinc concentrations have been known to be high, exposed mallard ducks to dietary concentrations of zinc ranging from 3,000 to 12,000 ppm. Severe mortality was noted in all exposed groups 30 days after initiation of the study. Table 2-2 lists some toxicity values for zinc in fish.

TABLE 2-2. Acute Toxicity Values for Fish

Species	Chemical form	Hardness (mg/L) as CaCO_3	LC50/EC50 ($\mu\text{g/L}$)
Rainbow trout <i>Salmo gairdneri</i>	Zinc sulfate	30	240-830
		47	370-517
		179	2,960
		333	7,210
Atlantic salmon <i>Salmo salar</i>	Zinc sulfate	14	420-740
Brook trout <i>Salvelinus fontinalis</i>	Zinc sulfate	47	1,550-2,120
		179	6,980
Goldfish <i>Carassius auratus</i>	Zinc sulfate	20	6,440
		45	7,550
Fathead minnow <i>Pimephales promelas</i>	Zinc sulfate	46	600
		203	8,400-13,000
Bluegill <i>Lepomis macrochirus</i>	Zinc sulfate	20	4,850-5,820
	Zinc chloride	20	5,370
		52	6,910-7,450
White perch <i>Morone americana</i>	Zinc nitrate	55	14,400
Striped bass <i>Morone saxatilis</i>	Zinc nitrate	55	6,800

Source: U.S. Environmental Protection Agency (1980).

3. Health Effects

3.1 PHARMACOKINETICS AND METABOLISM

3.1.1 Absorption

The absorption of zinc in humans and other mammals is similar. The site of absorption depends on the form of presentation. Inhaled zinc is absorbed across the alveolocapillary membrane; however, the fate of inhaled zinc will depend on the particle size and solubility as well as the functional state of the lungs. Orally administered zinc is absorbed across the gut mucosa with the major site of absorption in the second portion of the duodenum. Absorption across the tissue and organ membranes normally follows gastrointestinal absorption or parenteral administration. Zinc may also be absorbed across the broken and unbroken epithelial membrane (National Research Council, 1978; Nriagu, 1980b).

There are no quantitative data on the deposition and absorption of inhaled zinc compounds, but experiments on humans indicate that both zinc oxide dust and fumes of very small particle size are deposited in the alveoli (Bonner and Bridges, 1983; U.S. Environmental Protection Agency, 1980). That inhaled zinc is absorbed was shown by the finding of widespread distribution of zinc in the soft tissue and liver of a man accidentally exposed to radiolabeled zinc dust from an experimental reactor (Newton and Holmes, 1966) and increased plasma and serum zinc levels in exposed workers (Chmielewski et al., 1974a,b; Hamdi, 1969; Klucik and Koprdá, 1979; U.S. Environmental Protection Agency, 1980).

The absorption of orally ingested and parenterally administered zinc is affected by several factors, some of which include: the amount of zinc ingested, the zinc status of the organism, and the presence of other substances (Lykken et al., 1986; Song and Adham, 1985; van Rijn and Hall, 1985; Prasad, 1978; National Research Council, 1978; Nriagu, 1980b; Fickel et al., 1986; Furchner and Richmond, 1962).

A significant decrease in plasma, erythrocyte, and leukocyte zinc levels has been seen after experimentally induced zinc deficiency. Following oral zinc supplementation, values close to normal were obtained (Prasad et al., 1978). Spencer et al. (1986) found that intravenously administered zinc is rapidly distributed. Using radiolabeled zinc as an indicator, the zinc retention after 30 days was ≥ 80 percent. The zinc status of the subjects was not obtained prior to administration of the radiolabeled zinc. Istfan et al. (1983) found that absorption of radiolabeled zinc increased linearly with an increasing level of available zinc.

Valberg et al. (1985) studied the rate of absorption and retention of zinc in 20 healthy subjects. Subjects ingested 25 mg radio-labeled zinc in metal free water or in ground white turkey meat after overnight fasting. The absorption and retention of radiolabeled zinc after 7 days was 42 percent for both methods of administration. However, the rate of absorption, as shown by the average increase in plasma zinc levels over a 4-hour period was significantly

lower when zinc was administered in the solid test meal. The authors believed that this finding was the result of the binding of zinc to food and the slower rate of gastric emptying of the solid meal.

Hyperzincuria is associated with the consumption of alcohol. Dinsmore et al. (1985) after orally administering alcoholic and nonalcoholic volunteers 50 mg zinc supplements via diet found significantly higher serum zinc levels in the nonalcoholic volunteers. Under normal physiological conditions a mutual inhibition also exists between zinc and folic acid (Ghishan et al., 1986). Zinc absorption is reduced if the diet contains large amounts of phytate or phytic acids (Lowy et al., 1986; Solomons et al., 1979; Reinhold, 1971; Reinhold et al., 1973, 1974; Turnlund et al., 1984; Morris and Ellis, 1980). Since phytic acid and phytates are found in plants and seeds, zinc from plants is considered to be less available to monogastric animals than zinc derived from animal protein. This was suggested to be a contributing factor in the zinc deficiency seen in Iranian villagers who consumed a substantial amount of unleavened bread high in phytate.

A biological antagonistic relationship exists between zinc and several other metals. Generally calcium does not affect zinc absorption except in the presence of phytate (Spencer et al., 1984; Snedeker et al., 1982; National Research Council, 1978; U.S. Environmental Protection Agency, 1980) by forming an insoluble calcium-zinc-phytate salt at the site of intestinal absorption (Halsted et al., 1974; Forbes et al., 1983). There are, however, indications that high levels of calcium may affect zinc absorption when dietary levels of zinc are marginal (Halsted et al., 1974; National Research Council, 1978; Spencer et al., 1984). As such, the high level of calcium (18.6 percent) in clay ingested by Iranians with a history of geophagia may have been a contributing factor to the zinc deficiency seen in that group (National Research Council, 1978). Calcium has also been implicated in the formation of irreversible sickle cells in sickle cell anemia patients. Data on the interactions of zinc with calcium suggest that zinc may competitively inhibit calcium leakage into the red blood cells and inhibit the formation of the irreversible sickle cells (Prasad, 1978). Klucik and Kopra (1979) reported that exposure to levels of zinc ranging from an average of 0.5 mg/m³ to 7.14 mg/m³ produced signs of hypocalcemia in exposed workers. High levels of orally administered zinc decreases the retention of copper and if administered over an extended period of time will induce copper deficient anemia and neutropenia (Festa et al., 1985; Fischer et al., 1983, 1984; L'Abbé and Fischer, 1984). Mulhern et al. (1986) reported that excess dietary zinc (2000 ppm zinc/day) produced copper deficiency in the offspring of C57BL/6J mice. The offspring also developed alopecia by 5 weeks of age. In addition, the authors reported that excess zinc causes alopecia in the monkey and mink. Whether excess zinc administered at certain stages of development will produce alopecia in humans has not been determined. An increased ingestion of zinc will offer protection against some of the toxic effects of lead absorption (Nriagu, 1980a; Cerklewski and Forbes, 1976; El-Gazzar et al., 1977) by inhibiting lead absorption at the intestinal level (Cerklewski and Forbes, 1976). A nonheme iron and zinc ratio of 2:1 slightly inhibits zinc absorption (Solomons, 1986; Solomons and Jacob, 1981) by competing with zinc in the upper small intestine and delaying its absorption (Meadows et al., 1983). However, Solomons (1986) suggested that there are sufficient sites for both zinc and iron absorption when the total ion concentration does not exceed 25 mg. Cadmium, a nonessential and toxic metal is associated with zinc in both geological and biological matter. The interaction between cadmium and zinc has not been fully demonstrated; however, renal

concentrations of zinc have been shown to parallel those of cadmium up to concentrations of 50 to 70 $\mu\text{g/g}$. There are also equimolar amounts of cadmium and zinc in the kidney when cadmium levels are low, but as cadmium levels increase, the ratio of cadmium and zinc increases (U.S. Environmental Protection Agency, 1980).

Zinc may also be absorbed through both broken and unbroken skin (Hallmans, 1977; Derry et al., 1983; Anteby et al., 1978; Hallmans and Lasek, 1985). Hallmans (1977) found that serum zinc levels increased in burn patients treated with gauze containing zinc oxide. An increase in serum zinc levels was seen in healthy subjects treated with a zinc oxide ointment, but the increase was not statistically significant. It was theorized that zinc applied to subjects topically with normal serum zinc concentrations is bound in the hair follicles and slowly absorbed and stored or excreted resulting in no increase in serum zinc concentrations. (Derry et al., 1983). A slight rise in serum zinc has been seen in women using an intrauterine device containing copper and zinc (Anteby et al., 1978).

Numerous studies indicate that the body attempts to control the zinc balance homeostatically according to need by regulating the extent of absorption of dietary zinc and the rate of fecal excretion of stable zinc (National Research Council, 1978; Evans et al., 1973; Ansari et al., 1975, 1976; Weigand and Kirchgessner, 1978; Nriagu, 1980b; Cousins, 1985; Dinsmore et al., 1985). The exact mechanisms involved in homeostatic regulation have not been determined; however, recent information suggests that zinc absorption across the brush border surface of the small intestine may be partly regulated by a carrier-mediated diffusion mechanism which responds homeostatically to the dietary zinc supply (Cousins, 1986; Menard and Cousins, 1983b). It has also been reported that many brush border proteins are increased during zinc depletion (Menard et al., 1983); however, this finding has not been confirmed by other researchers (Park et al., 1985). Numerous other studies suggest that several proteins and low-molecular-weight compounds may be involved in the absorption of zinc and other heavy metals (Seal and Heaton, 1987; Wapnir and Stiel, 1986; Song and Adham, 1985; Wapnir et al., 1983; Lønnerdal et al., 1982; Menard and Cousins, 1983a; Freeman and Taylor, 1977; Smith et al., 1978; Blakeborough et al., 1983; Boosalis et al., 1983).

In examining the reason for the accumulation of metals in mammalian tissue a protein was discovered and termed metallothionein (Cousins, 1985). This low-molecular-weight protein is characterized by a very special amino acid complex consisting mainly of cysteine and a lack of aromatic amino acids and histidine (Nordberg and Kojima, 1978; Kojima et al., 1976). A more detailed discussion of the physical properties of metallothioneins are contained in Kagi and Nordberg (1979) and Cousins (1985). Metallothioneins have been isolated from intestine, liver, and kidney (Margoshes and Vallee, 1957; Kagi and Vallee, 1960). More recently, a metallothionein-like protein was isolated in the rat brain (Ebadi, 1984). The exact function of metallothionein has not been determined; however, several functions have been suggested. These include absorption and detoxification and hepatic storage of heavy metals (Jackson et al., 1986; Bell, 1979; Richards and Cousins, 1976; Cousins, 1985; Ebadi, 1984; Swerdel and Cousins, 1982; Menard et al., 1981; Olafson, 1983; Kern et al., 1981; Quinones and Cousins, 1984; Gallant and Cherian, 1986; Banerjee et al., 1982).

3.1.2 Distribution

The body of a 70-kg man contains approximately 1.4 to 2.3 g of zinc (Yamaguchi, 1984; National Research Council, 1978; Nriagu, 1980a; U.S. Environmental Protection Agency, 1980). Twenty percent of this value is thought to be present in the skin (Pories et al., 1967). In blood, zinc is present in the plasma, serum, erythrocytes, leukocytes, and platelets. Ohno et al. (1985) reported that out of the total zinc present in erythrocytes, 92.4 percent is bound in carbonic anhydrase isoenzymes and superoxide dismutase. The remainder is present in an available form or is attached to other enzymes. Leukocytes contain a zinc metalloprotein with no known enzymatic activity. Approximately 98.0 percent of the serum zinc is bound to proteins. Of the 98.0 percent protein-bound serum zinc, 85.0 percent is bound to albumin. The zinc binding to the albumin molecule may occur at any site where the imidazole groups are located (Foote and Delves, 1984). The remainder of the serum zinc is bound to α 2-macroglobulin, with the exception of a few percent which are bound to amino acids. Zinc in serum may be divided functionally into diffusible and nondiffusible fractions. The diffusible zinc in serum is that bound to amino acids and the freely exchangeable zinc from albumin. There is no exchange of zinc in the α 2-macroglobulin (Foote and Delves, 1984; Giroux et al., 1976; National Research Council, 1978). In plasma about 40.0 percent of the zinc is bound to α 2-macroglobulin. The remainder of the zinc is associated with plasma albumin (Failla et al., 1982).

In humans the highest concentrations of tissue zinc are found in the male reproductive system, notably in the prostate, where the concentration is approximately 100 μ g/g wet weight. Semen also has an extremely high zinc content, with concentrations ranging from 100 to 350 μ g/L (U.S. Environmental Protection Agency, 1980). Other tissues and organs with high concentrations of zinc include muscle, bone, liver, pancreas, kidney, hair, and some endocrine glands. The largest percent of the total body zinc is found in muscle and bone (Kiilerich and Christiansen, 1984). The average concentration of zinc in the liver is 55 μ g/g wet weight, which remains very constant during a lifetime (Elinder et al., 1977). Pancreatic zinc has a role in the production and function of insulin. In the kidney, zinc content will increase on an equimolar basis with an increase of cadmium up to a cadmium level of about 50 to 70 μ g/g (Elinder and Piscator, 1978; Piscator and Lind, 1972; Schroeder et al., 1967). The zinc content of hair has long been considered a good indicator of body zinc status. However, this test may not be as valid as once thought, since factors such as age and hair color may have a bearing on the zinc content of hair. Further, lower hair zinc levels have been found in pregnant and lactating women. Typical values for zinc concentrations in fresh tissues of several species are given in Table 3-1.

3.1.3 Elimination

Zinc is mainly excreted via the gastrointestinal tract. Fecal zinc varies with the zinc content of the diet; however, 70 to 80 percent of ingested zinc is found in the stool (Davies and Nightingale, 1975). Normally, urinary excretion of zinc is relatively minor: between 353 to 500 μ g of zinc per 24-hour period (Nriagu, 1980b; Henkin, 1971). Excessive urinary excretion of zinc results from abnormal excretion of molecules to which zinc binds and which prevent reabsorption, for example, albumin in nephrotic syndrome, chelating agents such as ethylenediamine (EDTA) (Nriagu, 1980b) and histidine and cysteine (Freeman et al., 1975; Rasmussen, 1982; Henkin et al., 1975; Yuncie et al.,

**TABLE 3-1. TYPICAL ZINC CONCENTRATIONS OF
NORMAL TISSUES IN FOUR SPECIES**

Tissue	Human μg/g	Monkey μg/g	Pat μg/g	Pig μg/g
Adrenal	12	16	--	33
Brain	14	--	18	--
Heart	33	22	21	--
Kidney	55	29	23	40
Liver	55	51	30	40
Lung	15	19	22	--
Muscle	54	24	13	--
Pancreas	29	48	33	45
Prostate	102	--	223	--
Spleen	21	21	24	28
Testis	17	17	22	--

Source: Underwood (1971)

1978). Also, Elinder et al. (1978) found that urinary excretion of zinc decreases after the age of 20 years.

In addition to fecal and urinary excretion, zinc is also excreted in sweat under conditions of extreme heat or exercise, via hair and milk, through placental transfer to the fetus, and via skin sloughing (National Research Council, 1978). Molin and Wester (1976) found the zinc content of the epidermis to be about 40 μg/g dry tissue by neutron activation analysis. They estimated the daily loss of zinc by desquamation to be from 20 to 40 μg. The mean loss of zinc in sweat has been reported to be 4 percent of the average daily intake (Jacob et al., 1981).

3.2 ESSENTIALITY AND BIOCHEMICAL ROLE

Over a hundred years ago zinc was shown to be an essential element in the nutrition of *Aspergillus niger*. It was not until some years later that the first indications of a function for zinc in plants and animals was uncovered. Zinc is necessary for the growth and development of humans and is included in the list of recommended dietary allowances (National Research Council, 1978; Krebs and Hambidge, 1986; U.S. Environmental Protection Agency, 1980) (Table 3.2).

The essential nature of zinc is based on its role as an integral part of some metalloenzymes, a cofactor in regulating the activity of zinc dependent enzymes (Nriagu, 1980b), and as a structural and functional component of biomembranes (Bettger and O'Dell, 1981). More than 20 zinc

Table 3-2. Recommended Dietary Allowances for Zinc

	Age (years)	Zinc (mg)
infants	0.0-0.5	3
	0.5-1.0	5
Children	1-10	10
Men	11-51 +	15
Women	11-51 +	15
Pregnant		20
Lactating		25

Source: National Research Council (1978).

metalloenzymes have been identified (Nriagu, 1980b) and over 100 enzymes require zinc for maximum catalytic function (Cousins, 1986) (Table 3-3 lists some of the zinc metalloenzymes). Zinc plays an important role in the metabolism of proteins and nucleic acids and is essential for the synthesis of DNA and ribosomal RNA. It also serves to stabilize the structure of some metalloenzymes. Thus the level of available zinc may control metabolic processes through the formation and/or regulation of the activity of zinc-dependent enzymes (Nriagu, 1980b).

3.3 CLINICAL MANIFESTATIONS OF ZINC DEFICIENCY

The metabolic and biochemical defects responsible for the symptoms of zinc deficiency are not fully understood. However, the manifestation of severe zinc-deficiency symptoms may be associated with the reduced activities of a number of zinc containing enzymes. Typical symptoms of zinc deficiency include: anorexia, pica, impaired taste acuity, mental lethargy, delayed sexual maturation in adolescence (Nriagu, 1980b), immune dysfunction (Fraker et al., 1986; Sandstead et al., 1982), dermatitis, emaciation, alopecia, ocular lesions, and retarded growth (Yamaguchi, 1984; Halsted et al., 1974). Chronic, severe, and untreated zinc deficiency can be fatal (Evans, 1986). Prasad et al. (1963) found that in certain villages in Egypt many people exhibited a syndrome characterized by dwarfism, anemia, hypogonadism, hepatosplenomegaly, rough and dry skin, and mental lethargy. Zinc deficiency was indicated by an abnormally low zinc content in plasma, red blood cells, and hair.

Less pronounced symptoms of similar syndromes have been observed in other parts of the world (Sandstead et al., 1982; Ghavami-Maibodi et al., 1983; Xue-Cun et al., 1985; Hambidge et al., 1972). In the U.S., Hambidge et al. (1972) saw evidence of zinc deficiency in children in Colorado using hair as an index. They found that out of 132 children, 10 had hair zinc levels below 70 µg/g. Nine of the 10 children had heights and/or weights in the lower range for their age group. Also, 5 of 6 children whose taste acuity was tested showed evidence of hypogeusia. Ghavami-Maibodi et al. (1983) reported on a group of healthy children who had hair zinc levels of < 140 µg/g

Table 3-3. Zinc Metalloenzymes

Enzyme	Source
RNA polymerase	<i>Escherichia coli</i>
RNA polymerase	T phage
DNA polymerase	<i>Escherichia coli</i>
Nucleotide pyrophosphatase	Rat liver
5'-Nucleotidase	<i>Escherichia coli</i>
Cyclic phosphodiesterase	<i>Escherichia coli</i>
Phosphomannose isomerase	Yeast
Phosphoglucomutase	Yeast
α -D-Mannosidase	Jack bean (<i>Canavalia ensiformis</i>)
β -Lactamase	<i>Bacillus cereus</i>
Protease	Snake venom
5'-Adenosine monophosphate aminohydrilase	Rat muscle
Collagenase	<i>Clostridium histolyticum</i>
Neutral protease	<i>Bacillus cereus</i>
Dipeptidase	Porcine kidney
Phospholipase C	<i>Bacillus cereus</i>
Dipeptidase	Mouse Ascites tumor
α -Amylase	<i>Bacillus subtilis</i>
D-glyceraldehyde-3P-dehydrogenase	Porcine muscle
Lactic dehydrogenase	Rabbit muscle
Malic dehydrogenase	Bovine heart
Glutamic dehydrogenase	Bovine liver
Transcarboxylase	<i>Proteus shermanii</i>
Pyruvate carboxylase	Yeast
Mercaptopyruvate sulfur transferase	<i>Escherichia coli</i>
Rhodanase (sulfur transferase)	Bovine liver
5- Aminolevulinic acid dehydratase	Bovine liver

Source: National Research Council (1978).

and bone ages of at least 2 years less than their respective chronological ages. These children also had low levels of growth hormone, testosterone, and somatomedin C. After oral zinc supplementation there was a significant increase in the growth rate. Growth hormone, testosterone, and somatomedin C levels increased with increases in hair zinc levels.

Experimentally induced zinc-deficient subjects experienced considerable weight loss. During the zinc depletion period thymidinekinase activity was not detected and there was a reduction in plasma alkaline phosphatase and plasma lactic dehydrogenase activity. Changes were also noted in the RNA and DNA ratio in the connective tissue (Prasad et al., 1978).

Whether zinc deficiency causes human reproductive or teratological effects has not been established; however, the possibility has been suggested based on the results of a number of animal studies (Lytton and Bunce, 1986; Styrd et al., 1986; Dreosti et al., 1986; Hurley and Swenerton, 1966; Hurley and Mutch, 1973; Hurley et al., 1971; Apgar, 1971; Hurley and Shrader, 1972). Lytton and Bunce (1986) reported that female rats maintained on a low zinc diet starting on day 10 of gestation usually experienced a prolonged fetal delivery period with prolonged periods of abdominal straining. Also, many pups were either stillborn or died shortly after birth. Hurley and Mutch (1973) found that rats maintained on zinc-deficient diets from day 6 to 14 of pregnancy exhibited an increased number of stillbirths and a high incidence of congenital malformations. Similar results were reported by Hurley et al. (1971). After maintaining rats on a zinc-deficient diet from day 0 to 21 of pregnancy, they found that about half of the fetuses were resorbed and that almost all of the remaining fetuses showed gross malformations.

A number of studies on the effects of zinc deficiency indicated that zinc is necessary for normal neurological development and function (Dreosti et al., 1986; Hurley et al., 1971; Hurley and Swenerton, 1966; Gordon et al., 1982; Lokken et al., 1973; Hurley and Shrader, 1972; Halas et al., 1979; Halas and Sandstead, 1975; Golub et al., 1985; Sandstead, 1986). Hurley et al. (1971) reported severe neurological effects in the form of hydrocephalus, anencephalus, hydranencephalus and exencephalus in litters of zinc-deficient mothers. Gordon et al. (1982) found that zinc-deficient rats were slower to explore the observation area and only explored a small portion of the area. Marginally zinc-deficient infant primates showed signs of lethargy, apathy, and hypoactivity (Golub et al., 1985). Similar findings have also been reported in humans suffering from zinc deficiency (Prasad et al., 1963; Henkin et al., 1975).

Certain evidence suggests zinc is essential for immune function (National Research Council, 1978; Sandstead et al., 1982; Bach, 1981; Beisel, 1982; Moynahan, 1975; Nriagu, 1980b). Successful results have been reported in infants with acrodermatitis enteropathica after zinc therapy (Chandra et al., 1983; Eckhart et al., 1977; Ecker and Schroeter, 1978; Nriagu, 1980b). Patients with iatrogenic zinc deficiency have developed a clinical picture similar to that of acrodermatitis enteropathica which has been alleviated with zinc therapy (Sandstead et al., 1982; Nriagu, 1980b). Chandra et al. (1983) reported that zinc deficiency increases vulnerability to *Listeria*, *Salmonella*, *Coxsackie virus*, and other pathogens.

It has also been suggested that zinc deficiency stimulates the production of endogenous free radicals in lung microsomes. The endogenous free radicals may then react with tissue components initiating lipid peroxidation and/or cross-linking of proteins leading to cell damage (Bray et al., 1986).

3.4 EFFECTS IN ANIMALS

3.4.1 Acute Toxicity

3.4.1.1 Inhalation. Lam et al. (1985) found functional, morphologic, and biochemical changes in the respiratory tract of guinea pigs exposed to 5

mg/m³ zinc oxide for 3 hours/day for 6 days. Vital capacity, functional residual capacity, and alveolar volume were decreased following the last exposure. Microscopic lesions in exposed animals consisted of inflammation of the proximal portion of the alveolar ducts and adjacent alveoli characterized by interstitial thickening, increased pulmonary macrophages and neutrophils in adjacent airspaces, and replacement of the alveolar squamous epithelium with cuboidal cells. In an earlier study, Lam et al. (1982) found that ventilation and lung mechanics in guinea pigs exposed to 7.8 mg/m³ zinc oxide for a single 3-hour exposure period were not significantly different from controls. A significant decrease was, however, seen in the functional residual volume.

The pulmonary response to zinc oxide fumes of 23 guinea pigs was studied by Amdur et al. (1982). The animals were exposed to approximately 1 mg/m³ of freshly formed zinc oxide. Respiratory measurements were made every 5 minutes for a 30-minute preexposure period, a 1-hour exposure, and a 1-hour postexposure period. Pulmonary response measurements included resistance, compliance, frequency, total volume, and minute volume. The only statistically significant effect noted by the end of the exposure period was a 9 percent decrease in compliance. One hour postexposure, compliance had decreased 16 percent below control values. To further examine the decrease in compliance, the experiment was repeated using 7 guinea pigs. The animals were again exposed to approximately 1 mg/m³ of freshly formed zinc oxide for 1 hour, followed by a 2-hour postexposure observation period. Unlike the first experiment, a statistically significant decrease in compliance was not noted by the end of the exposure period. However, by the end of the first hour postexposure period, the compliance had dropped 16 percent below control values. At the end of the second hour postexposure period, the compliance had decreased to 27 percent below control values. The decrease in compliance without a change in the airway resistance noted in these experiments reflects a response in the periphery of the lung, the primary site of deposition of submicron aerosols.

The ability of zinc oxide to alter pulmonary defenses was evaluated by Hatch et al. (1985). Ninety mice were treated with an intratracheal injection of 10 or 100 µg zinc oxide followed by exposure to group C *Streptococcus* sp. The severity of the infection was quantitated by the resulting mortality over a 15 day period. A significant number of mortalities was noted in both exposure groups (73 and 55 percent, respectively).

An intratracheal injection of 0.5 mg zinc oxide produced morphological changes in pulmonary alveolar macrophages (PAM) in rats. One week after exposure, PAM contained a prominent nucleolus within a vaginated nucleus. The resident pulmonary macrophages contained many electron dense structures, some of which were homogeneous and membrane bound, while others of varying electron densities were in the proximity to lamellar configurations. Membrane-bound electron dense structures were also seen in the intercellular spaces among interstitial macrophages. The authors hypothesized that the presence of electron dense structures along with lamellar membranous formation in proximity to and within the interstitial macrophages suggested a transfer of particulate matter from alveolar to the resident interstitial macrophages. Accumulation of particulate matter within the macrophages may interfere with the normal phagocytic function of these macrophages, resulting in the metal fume fever (see Section 3.10.1) associated with zinc toxicity (Migally et al., 1982).

Fischer et al. (1986) reported that zinc oxide is cytotoxic. Using the *in vitro* bovine pulmonary macrophage assay system, the EC₅₀ (effective

concentration required to reduce phagocytosis to 50 percent of control values) was 22 µg/ml.

Gupta et al. (1986) observed no signs of toxicity or symptoms of gross morphological changes in the lungs of guinea pigs 7, 15, or 30 days after a 50 mg intratracheal injection of zinc oxide dust. However, an increase in alkaline phosphatase activity was noted in the lung mitochondrial supernatant and serum. A decrease in the activity of lactate dehydrogenase in the lung mitochondrial supernatant was noted on days 7 and 15 postexposure, but became normal after 30 days. No significant change was observed in the activity of this enzyme in serum.

Conner et al. (1985) studied the irritancy potential of a combination of zinc oxide and sulfur dioxide. Guinea pigs were exposed to 6 mg/m³ zinc oxide mixed with 1 ppm sulfur dioxide for 3 hours a day for 6 days. Total lung capacity, vital capacity, functional residual volume, alveolar volume and diffusing capacity were decreased following exposure and had not returned to normal 72 hours after exposure. Morphological changes in the lungs were limited to the centriacinar alveolar ducts and associated alveoli and consisted of interstitial cellular infiltrate, increased numbers of macrophages in alveolar ducts and alveoli, and replacement of squamous alveolar epithelium with cuboidal cells. The severity and frequency of such lesions were lessened by 72 hours postexposure. Similar but more severe changes were seen after a single 3-hour exposure of 25 mg/m³ zinc oxide and sulfur dioxide (Conner et al., 1982).

A case of acute emphysema in cattle was reported by Hilderman and Taylor (1974). The episode occurred in a barn that was being remodeled. The cattle were exposed to zinc oxide fumes emitted during oxyacetylene cutting and arc welding of galvanized pipe. Three heifers were severely affected, and died within a short time. Autopsy findings showed severe changes in the lungs with edema, emphysema, and hemorrhages. Zinc concentrations in liver, kidney, and lungs were not above normal values in the two animals examined. In this case, a galvanized material was implicated, but the extremely severe condition caused by the fumes indicated either that cattle are highly sensitive to zinc oxide fumes, or that other metals, such as cadmium, may have been involved.

Harding (1957) administered intratracheal instillations of 50 mg of zinc stearate to rats. Approximately 50 percent mortality was noted after dosing. Surviving animals were sacrificed up to day 259 after instillation. Fibrosis could not be detected. Harding also found that the zinc stearate disappeared from the lungs of the survivors within 14 days after administration.

Unlike Harding, Tarasenko et al. (1976) found pathological changes in the lungs of surviving animals in the form of widespread plasmorrhagia in the walls of small arteries and alveolar atelectasis foci alternating with foci of chronic alveolar emphysema 2 months after a single 50 mg intratracheal dose of zinc stearate. Still later, chronic alveolar emphysema and bronchitis were seen.

3.4.1.2 Oral. In an outbreak described by Allen (1968), cattle were poisoned with dairy nuts which had been accidentally contaminated with zinc oxide. The zinc content of the nuts was 20 g/kg. Based on a dairy nut consumption of 7 kg/day, it is estimated that the cows consumed 150 g of zinc/day. Exposure was only for a couple of days, but it resulted in severe enteritis. On one farm 7 out of 40 cows were so severely affected that they died or had to be slaughtered. The postmortem examination revealed severe pulmonary emphysema, a flabby myocardium, blood spotting in the cortex

and medulla of both kidneys, and marked degenerative changes in the liver. The zinc concentrations in the two livers analyzed were extremely high, 1,430 and 2,040 mg/kg (dry matter basis), and there were indications that copper levels were lower than normal.

Breitschwerdt et al. (1986) described the clinical and laboratory findings of three cases of acute oral zinc toxicosis in dogs. In two of the cases the source of zinc was a metal nut high in zinc content (≥ 98 percent). In the third case, the animal had ingested a large amount of zinc oxide ointment which had been applied to the perianal and scrotum areas to prevent moist dermatitis secondary to fecal contamination. While only one dog succumbed to the zinc toxicosis, all of the animals exhibited a loss of appetite, weakness, depression, and vomiting. The zinc content in plasma and urine was also elevated over that routinely found in healthy animals. Necropsy findings in the dead animal were pulmonary peribronchial arteriolar thrombosis, enlargement of the right side of the heart, and various lesions of the kidneys. The zinc content of the liver and kidney was 369 (average 26.2) and 295 ppm (average 14.6 ppm), respectively.

3.4.2 Subchronic Toxicity

3.4.2.1 Inhalation. In a study designed to determine the effect of inhalation of zinc oxide particles of < 1 micron in size on rat lungs, Pistorius (1976) exposed test animals to 15 mg/m³ zinc oxide for 1, 4, or 8 hours/day for 84 days. There were no differences in lung function between controls and exposed animals except for a decrease in specific conductance and another lung function parameter termed "difference volume" (Δ -TGV- V_1) in the exposed groups at the end of the second week of the experiment. The conditions improved as the length of exposure increased. The author believed the improvement in lung function with the extension of exposure to be the result of an increase in macrophages, which in turn increased the elimination of zinc from the lungs. In another study rats were exposed to 15 mg/m³ zinc oxide dust for 4 hours/day 5 days/week for 1, 14, 28, and 56 days. Histological examination of the lungs showed core-shaped fresh leukocytic inflammatory changes with numerous small leukocyte plugs in the bronchus clearings and intraalveolar edema. After 14 days exposure isolated foam and round cell cores appeared. The inflammatory changes decreased by day 28 and 56; however, there were numerous alveolar macrophages (Pistorius et al., 1976).

Oberdorster and Hochrainer (1979) evaluated the effect of inhalation of zinc oxide aerosol on the lung clearance mechanisms. Rats were exposed to submicron zinc oxide aerosol (1 mg/m³) for 6 weeks followed by a 1-hour exposure to 11.5 mg/m³ ⁵⁹Fe as Fe₂O₃ (used as a marker). The rate of clearance of ⁵⁹Fe from the lungs of the zinc oxide exposed animals was found to be twice that of the controls. On day 38 postexposure, 62 percent of the initial lung ⁵⁹Fe was still present in the lungs of the zinc oxide exposed animals. The authors postulated that exposure to the zinc oxide aerosol over the 6 week period affected the bronchial and alveolar clearance mechanism.

3.4.2.2 Oral. Animals can tolerate high dietary levels of zinc without any signs of a toxic effect. Ansari et al. (1976) administered from 1,200 to 8,400 ppm zinc oxide to rats via their diet for 21 days. No clinical signs of toxicity were noted in any of the exposed groups. At the 1,000 ppm feeding level, Sutton and Nelson (1937) found no adverse effects in rats or their offspring. The National Research Council (1978) reported that dietary administration of 4,000 to 7,500 ppm zinc produced a condition resembling iron deficiency

anemia in young rats. Supplements of iron and copper increased the hemoglobin concentration to normal levels.

In 1937, the University of Illinois was asked to identify a disease in two suckling colts on a farm located near a zinc smelter. Autopsy examination of the colts revealed parasitism, a form of arthritis, and abnormal amounts of zinc in bone, liver, and urine. An abnormally high amount of zinc was also found in the mother's milk. Based on these findings, Graham et al. (1940) initiated a study to determine the effect of dietary zinc on pregnant mares and mares nursing colts. Mares were administered 3.5 and 35 g of zinc lactate via diet over a period of up to 2.5 years. These feeding levels were based on the zinc content of the feed assumed to have been consumed by the mares while suckling the affected foals. The results of the study did not demonstrate that zinc, at the levels administered, would produce harmful effects in pregnant mares or mares suckling colts. This led the authors to believe that the effects seen in the two colts were caused by something other than zinc. However, it should be pointed out that the zinc content in the milk from the experimental animals was less than that from the mares suckling the two infected colts.

The effects of subchronic exposure to zinc have also been studied in several commercial animal species. Sampson et al. (1942) evaluated the effect of ingestion of zinc lactate in pigs. In the first experiment shoats were fed a basal diet plus 100 g of zinc lactate for 3 months. At the conclusion of the experiment, none of the pigs showed any sign of an adverse effect. In the second experiment weanling pigs were fed a basal diet plus 17.5 g of zinc lactate for 9.5 months. The zinc-fed weanling pigs began losing their appetite after only a few weeks on the diet. Symptoms of stiffness and lameness were also noted. Autopsy findings revealed pathologic lesions in the joints and an increased liver zinc content. This arthritic condition was confirmed by Brink et al. (1959) and Hill et al. (1983) after feeding pigs from 500 to 8,000 mg/kg zinc. In addition to the arthritic condition characterized by swollen joints, at feeding levels of 2,000 mg/kg and above, test animals exhibited depressed weight gain and food consumption. There was also a dosage-related increase in deaths (Brink et al., 1959). Postmortem examination revealed extensive hemorrhaging in the axillary spaces and intestine and marked gastritis with some ulceration.

In sheep, the ingestion of 240 mg zinc/kg as zinc oxide or zinc sulfate administered three times a week for 4 weeks produced pancreatic damage in all exposed animals. Animals ingesting zinc sulfate also experienced severe diarrhea which commenced after a week of dosing and persisted throughout the experiment. All animals in the zinc sulfate group died after day 13. Postmortem examination revealed a reduction of the papillation of the rumen wall and edema of the fundic folds of the abomasum. The liver had a finely mottled surface and an orange brown color (Smith and Embling, 1984).

Dewar et al. (1983) studied the effects of excessive dietary zinc as zinc oxide in chicks and hens. Chicks were maintained on a diet containing 2,000, 4,000, or 6,000 mg/kg for 42 days or 1,000, 2,000, or 4,000 mg/kg for 28 days while hens received 10,000 or 20,000 mg/kg for 4 days. Mortality was high in chicks receiving 4,000 and 6,000 mg zinc/kg. Postmortem examination revealed macroscopic abnormalities of the alimentary tract. In five chicks in the 6,000 mg/kg group there was internal hemorrhaging from the descending aorta or the thoracic aorta. Histological examination revealed gizzard and pancreatic lesions in all exposed groups. There was no mortality reported for the exposed hens; however, gizzard and pancreatic lesions were found in both exposed groups.

3.4.3 Chronic Toxicity

No information was found on the effects of chronic inhalation exposure to zinc/zinc oxide in animals. However, a study on the oral administration of subtoxic levels of zinc indicates a possible effect on the endocrinological balance. Mice were administered 0.5 g/L zinc sulfate in drinking water for up to one year. The animals maintained a healthy outward appearance during the length of the study. Analysis of liver, spleen, and skin samples of zinc supplemented animals did not show a significant increase in zinc content over that of the controls. Histological examination revealed hypertrophy of the adrenal cortex and the pancreatic islets. Since hypertrophy of the adrenal cortex has been seen with an increased plasma level of certain pituitary hormones, it was suggested that the administration of zinc over an extended period of time may also cause hyperactivity of the pituitary (Aughey et al., 1977). In an earlier study, Drinker et al. (1927b) found no evidence of toxic effects in rats administered from 0.5 to 34.4 mg zinc/day as the oxide, citrate, acetate, and malate for a period of 35 to 53 weeks.

3.5 CARCINOGENESIS

Under conditions of high gonadal activity, the injection of zinc salts into the testes of fowl has induced testicular tumors (Sunderman, 1971; National Research Council, 1978; U.S. Environmental Protection Agency, 1980; Nriagu, 1980b). Seminomas, interstitial cell tumors, and teratomas have also been reported in rats after testicular injection of zinc salts (Nriagu, 1980b). Conversely, the injection of zinc sulfate into the mammary glands of young and sexually mature Marsh-Buffalo mice significantly delayed the onset and incidence of mammary adenocarcinoma (Bischoff and Long, 1939).

There is no evidence that the inhalation, ingestion, or parenteral administration of zinc induces the formation of tumors. There is, however, a considerable amount of information which indicates that the administration of zinc is indirectly involved in tumor formation as a growth promoter or inhibitor. In a study by Wallenius et al. (1979), 4-nitro-quinoline-n-oxide-induced cancer of the oral cavity in female rats appeared earlier in animals ingesting a diet containing 200 mg/kg zinc than animals fed 15 or 50 mg/kg zinc. Fenton and Burke (1985) found that TEPC plasmacytoma transplanted tumors were somewhat smaller in mice maintained on a zinc-deficient diet (0.5 µg/g) compared to mice maintained on a zinc-adequate diet (50 µg/g). Mathur et al. (1979) reported that zinc deficiency (5.9 mg/kg) promoted the development of 4-nitro-quinoline-n-oxide-induced histological changes of the oral cavity in rats. However, at the conclusion of the study there were no differences in tumor formation between the animals fed the zinc-deficient diet and the zinc-supplemented diet (260 mg/kg). Only moderate dysplasia was seen in animals on the zinc-adequate diet (50 mg/kg). The authors concluded that zinc deficiency facilitates the development of the initial histological changes and supplementary zinc provides an initial protective barrier against tumor formation, but once the protection is overcome, tumor formation is accelerated. Fong et al. (1978) found that a zinc-deficient diet (7 mg/kg) promoted the formation of methylbenzyl nitrosamine (MBN)-induced esophageal tumors. By the conclusion of the study, there was an increased incidence of esophageal tumors in zinc-deficient animals over animals maintained on the zinc-adequate diet (60 mg/kg). Similar results were reported by Gabriel et al. (1982) after maintaining rats on a zinc-deficient diet. In a more recent work, Fong et al. (1984) found that a zinc-

deficient diet also promotes the formation of benzylmethylamine (BMA)-induced esophageal tumors and NaNO_2 -induced forestomach tumors. Van Rensburg (1981), in a survey of 21 regions, found that in areas with high incidences of esophageal cancer consumed diets were deficient in zinc, magnesium, riboflavin, and nicotinic acid.

Many human studies have documented the level of zinc in both cancerous and noncancerous tissues, and the zinc content has been found to be both high and low with no definite pattern. Mulay et al. (1971) found a higher zinc content in bronchogenic carcinoma and cancerous breast tissue than in noncancerous bronchial and breast tissue. Lin et al. (1977) showed that zinc concentrations in the esophagus in humans with esophageal cancer were lower than normal. Zinc concentrations are normally very high in the prostate, but levels are consistently lower in carcinomatous prostate tissues (Lahtonen, 1985; Leake et al., 1984; Boddy et al., 1970; Feustel et al., 1982; Györkey et al., 1967; Schrodt et al., 1964; Habib et al., 1976). In the study by Habib et al. (1976), zinc concentrations in the neoplastic tissue of the prostate were less than half of those found in normal tissue or in hypertrophic prostates; however, cadmium levels were higher in the neoplastic tissue than in normal or hypertrophic tissue. High industrial exposure to cadmium has been implicated as a possible factor in the development of prostatic cancer.

The only positive carcinogenic response resulting from zinc occurs following injection of zinc salts into the testes of fowl and rats. The special situation with regard to injection site tumor has been reviewed by several authors. Gasso and Goldberg (1977) doubted the usefulness of the technique if only injection site tumors developed. Tomatis (1977) reviewed 102 chemicals reviewed by IARC that had been tested using the subcutaneous route. Based on the results by other routes, he concluded that "administration of a chemical by the subcutaneous injection route produced what one could call false negative results for six (5.6%) of the 102 chemicals tested, and if we accept all the criticism of this route of administration, false positive results for nine (8.7%) of the 102 chemicals tested." Thus, with this route a false positive result is a more likely result if only injection site tumors are observed. Recently, Theiss (1982), again using the IARC data base, concluded that subcutaneous injection was most useful if the compound produced tumors at a site distant from the site of injection. Therefore, by analogy one could conclude that the testicular tumors resulting from injection of zinc salts into the testes are of limited predictive value. In addition, with zinc it is possible that the resulting testicular tumors could be influenced (i.e., promoted) by the local displacement of cadmium from its carrier protein. Because the carcinogenicity data in animals is derived from an artificial exposure route and no other animal or human data exists to evaluate the carcinogenic potential, the available evidence for zinc and zinc oxide is considered to be inadequate, equivalent to a group D weight-of-evidence using EPA's Cancer Risk Assessment Guidelines.

3.6 MUTAGENICITY

In its review of zinc's possible mutagenic effects, the National Research Council (1978) found no literature suggesting that zinc or any of its compounds are mutagens. However, Voroshilin et al. (1978) reported chromosomal damage in the form of an increased frequency of hyperdiploid cells but not structural aberrations in the bone marrow of noninbred rats. The rats were exposed to 0.1 and 0.5 mg/m³ zinc oxide aerosol continuously for a period of 5 months. In the same report, the authors also found an increase in

the frequency of structural aberrations of the chromosomes and hyperdiploid cells when human lymphocytes at the G_0 stage of the cell cycle were exposed to the action of zinc acetate at concentrations from 7.0 to 20.0 $\mu\text{g/mL}$. An interpretation of this report is difficult because the category of aberrations referred to as hyperdiploid cells is not one used by cytogeneticists in this type of study. Additionally, in the *in vitro* study the frequency of structural aberrations at 20 $\mu\text{g/mL}$ was slightly less than the frequency at 7 $\mu\text{g/mL}$ (3.6 percent versus 4.0 percent, respectively). In a recent study, Crebelli et al. (1985) found zinc oxide (1,000 to 5,000 $\mu\text{g/plate}$) nonmutagenic in the Salmonella reversion assay.

3.7 TERATOGENICITY

There are no data indicating that zinc is teratogenic. A greater risk of malformations is expected in regard to zinc deficiency, as discussed in Section 3.3. Zinc also appears to offer a degree of protection against the teratogenic effect of cadmium. In a study by Fern and Carpenter (1968), an increase in both unilateral and bilateral cleft lips and incomplete and complete palatal clefts was seen in the offspring of hamsters administered cadmium intravenously at levels of 2 and 4 mg/kg during the eighth day of gestation. The simultaneous administration of zinc sulfate was found to reduce the teratogenic effect of cadmium. This protective effect was also noted when zinc was administered 15 minutes to 6 hours after the cadmium; however, the malformations were slightly increased.

3.8 REPRODUCTION

It has been established that zinc deficiency may impair normal reproduction or adversely affect the outcome of pregnancy in humans and lower animal forms. However, excessive dietary zinc may also adversely affect fertility (Samanta and Pal, 1986; White, 1955) and pregnancy (Sutton and Nelson, 1937; Schlicker and Cox, 1968; Hill et al., 1983; Kumar, 1976). Samanta and Pal (1986) reported that sperm motility was inhibited in rats fed a diet containing 4,000 ppm zinc for 30 to 32 days. Of 18 females mated with males from the zinc-exposure group, only 11 females conceived, whereas all of the females (15) mated with control rats conceived. No stillbirths or malformations were reported in either group. Sutton and Nelson (1937) found that in most cases growth was retarded and no reproduction occurred after feeding female rats 10,000 ppm zinc carbonate. At the 5,000 ppm feeding level, increased stillbirths occurred. Growth and reproduction were not affected at the 1,000 ppm feeding level. The original females were remated. At the 5,000 ppm level, no live young were born and, after 5 months, the females ceased to become pregnant. Hemoglobin values were found to decrease with time in the 5,000 ppm group. Hemoglobin and red blood corpuscles were diminished in those animals in the 10,000 ppm feeding group. Schlicker and Cox (1968) reported 100 percent resorption of fetuses in rats fed 4,000 ppm zinc oxide beginning 21 days before gestation. Kumar (1976) found a significant number of resorptions in rats receiving a total of 180 ppm zinc daily. In a brief statement this author also reported that three premature births and one stillbirth occurred in a small group of women given 100 mg zinc sulfate (40.5 mg zinc) daily during the third trimester of pregnancy. However, no premature births or stillbirths were reported in a group of seven women receiving 200 mg zinc sulfate twice a day (81 mg zinc/day) during the third trimester of pregnancy (Nriagu, 1980b). Also, adverse effects on the outcome of pregnancies were not reported in a group

of women supplemented with 20 mg zinc sulfate per day in addition to dietary zinc intakes of from 9.3 to 11.3 mg/day (Hunt et al., 1985).

3.9 NEUROTOXICITY

It is known that zinc deficiency may have an adverse effect on the central nervous system. However, recently it has been suggested that the ingestion of excessive amounts of zinc may also exert toxic effects on the central nervous system. Kozik et al. (1980) found morphological changes in the ammal cortex and basal ganglia in the form of shrunken neurocytes accompanied by proliferated oligodendroglia, neuronal losses, and degenerative changes and considerable vacuolization of the neurocytes of the septum lucidum amygdaloid body in rats orally dosed with 100 mg zinc oxide for 10 days. A reduction in the activity of acid phosphatase (acP), adenosine triphosphatase (ATPase), acetylcholinesterase (AChE), and butyrylthiocholinesterase (BuTJ) along with an increase of thiamine pyrophosphatase (TPPase) and nonspecific esterase (NsE) activity was also noted. The authors stated that the effects seen were rather low grade and may be reversible. In a similar study, Kozik et al. (1981) found that the ingestion of large doses of zinc oxide increased the production of neurosecretion in the hypothalamus (supraoptic and paraventricular nuclei) along with an increased release of antidiuretic hormone in the neurohypophysis. Histological examination of cells of the hypothalamic nuclei revealed enlargement of both the cells and their nuclei. Many neurocytes of the supraoptic and paraventricular nucleus were also shrunken. Motor effects suggestive of neurological disturbances in pigs during zinc intoxication have also been reported (Hill et al., 1983).

3.10 EFFECTS IN HUMANS

The literature on adverse health effects in humans resulting from exposure to excessive amounts of zinc is limited. One probable reason is that zinc has generally been accepted as a beneficial substance, and adverse effects, with the exception of those incurred under occupational settings, have generally not been expected or sought.

3.10.1 Inhalation Toxicity

In certain occupational settings, the inhalation of zinc oxide fumes produces a disease known as metal fume fever. This disease is produced by the inhalation of zinc oxide fumes when zinc is heated in an oxidizing atmosphere to a temperature near its boiling point, as in smelting operations, galvanizing, brass-founding, brazing, and oxyacetylene welding of galvanized iron. Metal fume fever generally strikes at the beginning of the work week when the worker has not been exposed for a couple of days, and so it has been called "Monday Fever." Further repeated exposure does not cause any new symptoms, suggesting some type of adaptation. The symptoms of this disease (headache, fever, hyperpnea, nausea, sweating, and muscle pains) occur within a few hours after exposure and may persist for 1 to 2 days. The most prominent laboratory finding is leucocytosis. While metal fume fever is most commonly caused by exposure to zinc oxide fumes and/or dust, it may also be caused by exposure to other metals such as manganese, copper, iron, cobalt, cadmium, antimony, lead, and beryllium. Most of our knowledge about metal fume fever and its relationship to zinc oxide fumes comes from the beginning of the century (Drinker et al., 1927a, 1928; Sturgis et al., 1927). Many reviews on metal fume fever, often

containing case reports, have also been published (Anseline, 1972; Armstrong et al., 1983; Wolf, 1975; Kemper and Trautman, 1972; Prasad, 1978; Hegsted et al., 1945; Kehoe, 1948; Rohrs, 1957; Summer and Haponick, 1981; Mueller and Seger, 1985).

There are few data on the ambient levels of zinc oxide fumes that might cause metal fume fever in man. Sturgis et al. (1927) exposed two people to zinc oxide fumes at a dose corresponding to 600 mg zinc/m³. It was calculated that the subjects inhaled 48 and 74 mg zinc, respectively. Both subjects developed symptoms of metal fume fever. Batchelor et al., 1926; Kemper and Trautman (1972); and Hammond (1944) reported that metal fume fever does not occur at zinc oxide levels below 15 mg/m³.

Several theories have been postulated concerning the mechanism of metal fume fever, but there is no definite evidence for any of the proposed theories. McCord (1960) suggested that there is an allergic basis for the mechanism of the fever. Mori et al. (1975) stated that catalytically active metal oxide fumes produced by heating the metal within the proper temperature range in the presence of carbon monoxide causes metal fume fever by an oxidative action in the blood. Regardless of the mechanism of the fever, the disease is likely caused only by metal particles of extremely small size. These penetrate deep into the alveoli, causing acute reactions there (National Research Council, 1978; U.S. Environmental Protection Agency, 1980).

Acute pulmonary damage that can be lethal may occur after the inhalation of zinc chloride, the major component in smoke coming from the so-called "smoke bombs" often used in military exercises. Inhalation of such smoke in confined spaces may rapidly lead to severe pulmonary disease (Milliken et al., 1963; Schmahl, 1974; Schenker et al., 1981). Milliken et al. (1963) reported on a fire fighter who died after being exposed to zinc chloride smoke from a smoke generator during a demonstration. The subject experienced difficulty in breathing, tachypnea, epigastric pain, nausea, and fever followed by cyanosis, confusion, and coma. Postmortem examination revealed advanced pulmonary fibrosis, acute cor pulmonale, and right ventricular hypertrophy. Death was attributed to acute respiratory insufficiency.

The effects of inhalation of zinc chloride in smoke from smoke bombs have also been described by Schmahl (1974), who reported on 11 cases, of which 2 had very severe reactions. There were no severe sequelae; however, in one case it was almost 2 years before the lung function returned to normal.

3.10.2 Oral Toxicity

The hazards of ingesting foods and/or liquids stored in galvanized containers are well known. Callender and Gentzkow (1937) reported on a case of two companies of soldiers that dined separately who became ill after consuming limeade which had been prepared and stored in galvanized iron cans. Symptoms included gastrointestinal distress and diarrhea of mild intensity. Analysis of the limeade prepared under the same conditions as that in the poisoning incidents revealed a concentration of zinc oxide of 910 mg/L and 15.6 mg/L of antimony. It was concluded that the amounts of zinc and antimony present in the limeade were responsible for the poisonings. Brown et al. (1964) reported on two cases of zinc poisoning in California. In the first case, 300 to 350 people became ill after consuming food which had been stored in galvanized containers. By simulating the preparation and storage of the contaminated foods, the investigators estimated that the zinc

concentration approached 1,000 ppm (wet weight). In the second case, 44 people became ill with nausea, vomiting, and diarrhea within 20 minutes after consuming an alcoholic punch. Analysis of the punch revealed that it contained 2.200 mg/L of zinc. A group of students in a home economics class experienced chills, dizziness, nausea, vomiting, and headache after consuming fruit punch which had been stored in a galvanized container overnight. Punch samples from the storage container contained 443 ppm zinc (Lapham et al., 1983).

Hooper et al. (1980) after orally administering 440 mg zinc sulfate/day (160 mg elemental zinc/day) to healthy young males for 5 weeks found a 25 percent reduction in the high-density lipoprotein-cholesterol (antiatherogenic lipoprotein) levels. The authors speculated that excessive levels of orally administered zinc may be atherogenic in man. The effect of moderate increases in dietary zinc on the high-density lipoprotein-cholesterol level is not known.

In a later work, Chandra (1984) found a reduction in the high-density lipoprotein-cholesterol level and an increase in the low-density lipoprotein-cholesterol level in healthy adult males after oral administration of 150 mg elemental zinc/day for 6 weeks. A reduction in lymphocyte stimulation to phytohemagglutinin and a reduction in polymorphonuclear-migration in response to chemotactic migration and phagocytosis of bacteria was also seen in these subjects. The results of this study indicate that oral ingestion of excessive amounts of zinc by healthy individuals over an extended period of time may have a deleterious effect on both the immunologic and cardiovascular systems.

Murphy (1970) reported on a 16-year old boy who ingested 12 grams of zinc over a 2 day period to hasten healing of a minor laceration. Three days after ingestion the subject experienced difficulty in awakening after a full night's sleep, light-headedness, slight staggering of gait, and difficulty in writing. Follow-up examination 1 month later revealed no apparent sequelae.

3.10.3 Other Routes of Exposure

Because it is an essential element, zinc is routinely added to parenteral nutrition regimens; however, care must be taken to ensure against zinc intoxication. Brocks et al. (1977) reported on a woman who suffered from a case of acute zinc poisoning while receiving total parenteral nutrition. Over a period of 64 hours she received 7.4 g of zinc sulfate. The patient became ill with pulmonary edema, jaundice, vomiting, diarrhea, and oliguria. Her serum zinc concentration was 4,184 $\mu\text{g}/100\text{ mL}$. In spite of treatment, renal function did not improve and she remained oliguric. She died after 47 days of illness with bronchopneumonia.

Gallery et al. (1972) reported on a patient who became ill with nausea, vomiting, and fever during home hemodialysis. An investigation into the cause of the illness disclosed that the patient was using rain water stored in galvanized tanks for the dialysis. The water contained 625 μg zinc/100 mL.

3.10.4 Epidemiology

In 1926, Batchelor et al. made an extensive investigation of workers exposed to zinc in a smelter in New Jersey. A total of 24 workers were selected from a baghouse where zinc oxide was handled, from several zinc oxide packing plants, from a plant handling metallic zinc, and from a lithopone packing house. The length of exposure ranged from 2 to 35.5 years. In most

work places the mean zinc concentrations were generally below 35 mg/m³, except in the zinc dust plant, where concentrations of up to 130 mg/m³ were measured.

The 24 subjects underwent careful examinations. A slight leukocytosis was seen in 14 of the subjects. Hemoglobin readings ranged between 72 and 97 with the average being 81. Zinc in whole blood in the exposed groups averaged 458 µg/100 mL, compared to 387 µg/100 mL in controls. In exposed groups, 24-hour zinc elimination via feces averaged 46.8 mg, while in controls the average was 9.32 mg. This finding indicated an exposure via the gastrointestinal tract. The conclusion of the authors was that workmen could be exposed to zinc compounds in a smelter for decades without any symptoms or chronic disease. However, more recent surveys, discussed below, do indicate hazards associated with high-level exposures to zinc compounds in the workplace.

Chmielewski et al. (1974a,b) examined a group of workers in a shipyard consisting of ship smiths, electric welders, ship's pipeline fitters, and zincifying workers who were exposed to zinc oxide (see Table 3-4). Exposure levels varied and in some cases exceeded the maximum acceptable concentration (MAC) for zinc oxide in air (5 mg/m³). The highest concentrations of zinc oxide during work were found at the stands of the electric welders who worked in containers (maximum 58 mg/m³, mean 18 mg/m³), the ship's pipeline fitters working within the engine room of the ship (maximum 40 mg/m³, mean 5 mg/m³), and the ship smiths employed in a superstructure (maximum 50 mg/m³, mean 12 mg/m³). Interviews showed that most of the smiths, welders, and fitters had experienced metal fume fever several times. Frequent occurrences of chronic respiratory tract infections were noted in the welders and fitters during the physical examination. Two cases of an early stage of welder's pneumoconiosis were noted in the welders' group. Chronic conjunctivitis and dermatitis occurred in all groups examined. Chronic gastritis was noted in all groups examined; however, because of the lack of a commonly accepted objective diagnostic criterion, an unequivocal confirmation of this diagnosis could not be made. A statistically significant increase in aspartate aminotransferase activity was noted in the welders and a statistically significant rise in alanine aminotransferase was also noted in the welders and fitters. However, these workers were also exposed to other hazardous compounds, such as nitrogen oxides.

Bobrishchev-Pushkin et al. (1977) studied the health status of 1,018 workers in the casting shops of three copper alloy production facilities. Four hundred and fifty-one workers from the rolling shops were used as controls. The average level of zinc oxide exposure in the casting shop was 2.1 mg/m³ (range of 0.2 to 5.1 mg/m³). Analysis of the health status of workers over a 5 year period showed an increased illness rate for the respiratory organs such as subatrophic changes in the breathing passages, chronic bronchitis, and diffuse pneumosclerosis. The frequency of illness with subatrophic and atrophic rhinitis, rhinopharyngitis, and rhinopharyngolaryngitis increased with the length of employment. The illnesses were noted in 15 percent of those with an employment of 10 years, in 21 percent with 11 to 20 years of employment, and in 35 percent of those employed for over 20 years; these illnesses were 3 to 6 times higher than for controls. Chronic bronchitis was diagnosed in 11 percent of exposed workers compared to 6 percent in controls. However, workers were also exposed to other metals such as copper, lead, and nickel.

A study of the mutagenic potential of urine from subjects occupationally exposed to a variety of compounds, including zinc oxide in the rubber

Table 3-4 Groups Involved, Age, Duration of Work and Timing of Work of the 66 Workers Exposed to the Effect of Zinc Oxide- Seen for Medical Examination

Number of the workers examined	Groups examined	Shop	Working stand	Average age of the groups examined (yr)	Mean duration of professional work (yr)	Mean duration of exposure to zinc oxide	
						(yr)	daily (hr)
20	ship-smiths	k-3	super-structure	27.6	7.0	3.0	4.2
13	electric welders	k-3	super-structure container	29.0	8.0	6.0	4.6
15	ship's pipe-line filters	R	engine-room	29.2	7.9	7.1	3.7
18	zincifying workers	I	zincifying shop	36.6	14.5	8.5	6.0

Source: Chmielewski et al. (1974b)

industry, was conducted by Crebelli et al. (1985). The urine samples were found to not be mutagenic in the microtitre fluctuation assay with *Salmonella typhimurium* strains TA1535, TA98, and TA100.

Klucik and Koprdá (1979) found that everyone exposed to zinc oxide dust in a zinc oxide factory showed signs of hypocalcemia. Exposure levels were reported to average 0.5 mg/m³ for zinc melters and 2.44 to 7.15 mg/m³ for zinc oxide packers; however, it was not indicated how these values were obtained. Serum calcium levels of exposed subjects were significantly lower and serum zinc was higher than in controls. X-rays revealed definite signs of osteoporosis, loss of spongiosis in the vertebrae and pelvis of two of six zinc oxide packers, of which one was thought to be due possibly to the age of the subject (60 years). The authors suggested that with a higher zinc intake, the zinc forces calcium from the bone, and the latter is then eliminated.

In a study on furnace operators exposed to zinc oxide fumes in a brass foundry for a mean duration of 11 ± 5 years, Hamdi (1969) found that workers often complained of epigastric pain. These workers showed a statistically significant increase in zinc concentration in whole blood, blood corpuscles, and basal fasting gastric juice in comparison to nonexposed subjects. The author suggested that the increased zinc content of the gastric juice may have been responsible for the gastric complaints; however, it could also be due to the presence of other substances used in the manufacture of the alloys.

Zinc stearate, an organic compound of zinc encountered in the rubber and plastics industry, is suspected of causing lung disease. Uotila and Noro (1957) reported on the death of a man who had been employed in the rubber industry for 29 years. The cause of death was determined to be chronic pneumoconiosis. Histochemical examination of the lungs showed an increased deposit of zinc; however, no quantitative determination of the zinc content was made. The role of zinc stearate as the causative agent in pneumoconiosis has also been evaluated by Weber et al. (1976). Weber and co-workers, as reported by the U.S. Environmental Protection Agency (1980), described the autopsy findings in a man who, for the last 8 years of his life, had been exposed to zinc stearate in the plastics industry. Pneumoconiosis was given as the cause of death. The lungs contained 62 mg/kg zinc on a dry weight basis, which was within normal limits. The authors concluded that zinc stearate could not have caused the fibrosis. However, as pointed out by Harding (1957), zinc stearate is relatively rapidly removed from the lungs; thus, a normal content of zinc does not exclude the possibility that zinc may have contributed to the disease.

4. References

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